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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,466	09/19/2006	Mariusz W. Szkudlinski	TROP-001/01US 304828-2046	9091

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EXAMINER	
BORGHEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,466	SZKUDLINSKI ET AL.	
	Examiner	Art Unit	
	CHRISTINA BORGEEST	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-40,43,47-67,84-99,102-115,118-129,132,133 and 136-138* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 7-10,13,14,16-25,29-39,47-51,53-57,59-66,94,96,102,103,110,112,118,119,124-126,132 and 133.

Continuation of Disposition of Claims: Claims rejected are 1-6,11,12,15,26-28,40,43,52,58,67,84-93,95,97-99,104-109,111,113-115,120-123,127-129 and 136-138.

DETAILED ACTION

Response to Amendment

Applicant's amendment filed 15 February 2011 is acknowledged. Claims 1, 12, 14, 17, 19, 21, 23, 25, 28, 29, 32, 34, 37, 39, 43, 109, 137 and 138 are amended. Claim 44-46 are newly canceled and claims 41, 42, 68-83, 100, 101, 116, 117, 130, 131, 134 and 135 were previously cancelled. Claims 7, 8, 9, 10, 13, 14, 16-25, 29-39, 47-51, 53-57, 59-66, 94, 96, 102-103, 110, 112, 118-119, 124-126, 132, and 133 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b).

Claims 1-6, 11, 12, 15, 26-28, 40, 43, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129 and 136-138 are under examination.

Formal Matters

It is noted that claim 137 has been amended to replace the comma at the end of the claim with a period. Since claim 137 has been amended it should be denoted has having a status of "currently amended," not "previously presented." Further, the text of any added subject matter must be shown. In the instant case, since the change involves fewer than five consecutive characters, double brackets may be placed before and after the deleted characters. See CFR 1.121.

Objections/Rejections Withdrawn

Note: All rejections made over claims 44-46 are hereby withdrawn in response to Applicant's cancellation of those claims.

Claim Objections

The objection to claims 1, 137 and 138 for informalities is withdrawn. Specifically, the objection to claim 1 for the recitation in line 6 the "a" in the phrase "a ten fold" for being awkward grammatically is withdrawn in response to Applicant's amendment of the claim to recite "at least about ten fold". Further, the objection to claim 137 for not having a period at the end of the claim is withdrawn in response to Applicant's amendment. Finally, the objection to claim 138 for reciting "FSG" in line 2 of the claim instead of "FSH" is withdrawn in response to Applicant's amendment to recite "FSH" in line 2.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 1-6, 11, 12, 15, 26-28, 40, 43, 52, 58, 67 and 109 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. Specifically, claim 1 has been amended to recite "FSH comprising a modified α-subunit and a modified β-subunit, wherein the modified β-subunit", which clarifies the language of the claims. Claim 12 has been amended to indicate that said basic amino acids at positions 16 and 20 are substituted with an arginine. Claim 28 has

been amended to indicate said basic amino acids at positions 13, 14, 16 and 20 are substituted with an arginine. Claim 43 has been amended to indicate said basic amino acid at position 4 is substituted with an arginine. Claim 109 has been amended to indicate the phrase "contains an arginine at positions 13, 14, 16 and 20" refers to the α-subunit.

Rejections Maintained

Note: Response to Applicant's arguments is in the immediately following section.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-6, 11, 12, 15, 26-28, 40, 43-46, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129 and 136-138 under 35 U.S.C. 103(a) as being unpatentable over either Szkudlinski et al. (WO97/42322, US HEALTH published 13 November 1997) or Szkudlinski et al. (U.S. Patent Publication 2002/0110909, published 15 August 2002) and further in view of Schambye et al., (Patent Publication No. 2002/0127652, published 12 September 2002) is maintained for reasons of record and the following. All references are of record.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 1-6, 11, 12, 15, 26-28, 40, 43, 52, 58, 67 and 136-138 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-45 of U.S. Patent No. 7,070,788 in view of Schambye et al. (cited above) is maintained for reasons of record and the following.

Response to Arguments

It is noted that Applicant intended to apply the arguments regarding Schambye to both the claim rejections under 35 USC § 103 and the obviousness type double patenting rejection (see p. 21 of Applicant's remarks, "[f]or the reasons discussed above for the 103(a) rejections, Applicants respectfully disagree and request withdrawal of this rejection."). In a similar fashion to Applicant, the Examiner has addressed Applicant's arguments together.

Applicant argues at p. 19 that the substitution of the lysine residues are made for the purpose of introducing amino acid residues comprising an attachment group for a non-polypeptide moiety to prolong the half life of FSH, thus one of ordinary skill in the art would not have even thought of substituting arginine residues for the lysine residues of Schambye since the introduction of arginine would not have lead to the generation of better attachment residues for any non-polypeptide moiety since lysine is a much better attachment residue than arginine.

This argument has been fully considered, but is not found persuasive. First, as noted at p. 9 of the previous Office action, paragraph [0044] teaches a list of conservative amino acid substitutions that includes both arginine and lysine. Second, as noted at p. 9 of the previous Office action, paragraph [0120] of Schambye teaches that arginine is an appropriate substitute for lysine in the contemplated amino acid positions. Specifically, paragraph [0120] states "a modified FSH-α and/or a modified FSH-β, which differs from the corresponding hFSH-α/β in at least one introduced and at least one removed lysine residue," wherein the removal of a lysine residue is selected from "the group consisting of K45(a), K63(a), K75(a), K91(a) K46(b), K54(b), K86(b), and K110(b)," and further that "the removal preferably being achieved by substitution by any other amino acid residue, in particular by an arginine residue." As noted in the emphasis added above by the Examiner, Schambye explicitly teaches that residue 63 of the β-subunit can be substituted with arginine, and residue 63 of the β-subunit is recited in claims 1, 84, 104 and 120 as a residue that can be substituted with arginine. Thus there is an explicit teaching in the prior art of Schambye that overlaps with the independent claims.

Regarding the argument that the introduction of arginine would not have lead to the generation of better attachment residues for any non-polypeptide moiety since lysine is a much better attachment residue than arginine, Applicant has offered only argument, but no evidence that this is so. See MPEP 716.01(c) and 2145: The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). In re Geisler, 116 F.3d 1465, 43

USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the Applicant. In an attempt to verify Applicant's assertion, the Examiner found instead that Nissen et al. (U.S. Patent No. 6,555,660, issued 29 April 2003) teaches at column 5, suitable amino acids to which non-peptide moieties can be attached include arginine.

Applicant argues at p. 19 that they have solved the problem relating to potency and have generated FSH analogs that are at least about 10 fold more potent than wild type FSH. Therefore, Applicant asserts, it would NOT have been obvious to substitute arginine at positions 2, 4, 64, 67 and 69 of the modified β-subunit of Schambye, because adding an arginine instead of a lysine would not lead to the introduction of glycosylation sites and therefore would not be expected to enhance the stability of the β-subunit as was the aim of Schambye.

This argument has been fully considered, but is not found persuasive. First, one of the goals of Schambye was to increase circulating half-life, and the instant claims also recite such a goal; see for instance, claim 52. Further, the instant claims recite PEGylation of the FSH agonists. Thus the goals of Schambye and the instant claims are not at odds. Second, at paragraph [0120] Schambye teaches "a modified FSH-α and/or a modified FSH-β, which differs from the corresponding hFSH-α/β in at least one introduced and at least one removed lysine residue," wherein the removal of a lysine

residue is selected from "the group consisting of K45(a), K63(a), K75(a), K91(a) K46(b), K54(b), K86(b), and K110(b)," and further that "the removal preferably being achieved by substitution by any other amino acid residue, in particular by an arginine residue." As noted in the emphasis added above by the Examiner, Schambye explicitly teaches residue 63 of the β-subunit can be substituted with arginine, and residue 63 of the β-subunit is recited in instant claims 1, 84, 104 and 120 as a residue that can be substituted with arginine. Thus there is an explicit teaching in the prior art of Schambye that overlaps with the independent claims, namely substitution of arginine for lysine in residue 63.

Third, regarding the argument that the introduction of arginine would not lead to the introduction of glycosylation sites and therefore would not be expected to enhance stability, Applicant has offered only argument, but no evidence that this is so. Again, Nissen et al. (U.S. Patent No. 6,555,660, issued 29 April 2003) teaches at column 5, that arginine is a possible amino acid for attachment of an oligosaccharide moiety. Schambye explicitly teach the same substitution (arginine) to residue 63 of the β-subunit. Further, Schambye explicitly teaches at paragraph [0044] that lysine and arginine represent preferred conservative amino acid substitutions. The person of ordinary skill in the art would be motivated to make the substitutions based upon the general teachings of Schambye. The fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art, namely, greater potency of the FSH analogs, cannot be the basis for patentability when

the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues at p. 19 through p. 20 that contrary to the Examiner's assertion, nowhere does Schambye teach a method for constructing "superactive analogs of human glycoprotein hormones," and that Schambye does not use the term "superactive analog," further explaining that the Examiner's citation of claim 79, and paragraphs [0012], [0025], [0077] and [0078] of Schambye do not support of her assertion, but rather only states that the modified subunit of Schambye is stated to have the biological activity of native FSH, but a prolonged circulating half life.

This argument has been fully considered but is not found persuasive. In paragraph [0012], Schambye was not discussing the biological activity of their own modified subunit, but rather that of the prior art (citing prior art patents as part of a background section, not their own work). There is no evidence or teaching in Schambye that following the suggestion of the prior art would lead to an FSH with only the biological activity of native FSH. It is noted, that the Examiner erred in stating that Schambye taught "superactive analogs"; rather the teaching of "superactive analogs" and the corresponding claims and paragraph numbers can be found in the Szkudlinski references, particularly, the PGPUB, 2002/0110909. Nevertheless, the important issue raised by the Examiner in the previous Office action remains, namely that Schambye explicitly teaches the same substitution (arginine) to residue 63 of the β-subunit and further, Schambye explicitly teaches at paragraph [0044] that lysine and arginine represent preferred conservative amino acid substitutions. As noted in the previous Office action at pages 11 and 12, the person of ordinary skill in the art would be motivated to make the substitutions based upon the general teachings of Schambye because he or she would recognize the simple substitution of one known element,

namely a basic amino acid arginine for another basic amino acid, lysine, to obtain predictable results. The prior art suggests that in choosing between arginine and lysine, one of ordinary skill in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. The level of skill in the prior art is high with respect to FSH variants and the substitution of basic amino acids such as lysine and arginine. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art, namely, greater potency of the FSH analogs, cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues at p. 20 that contrary to the Examiner's assertion, Schambye does not teach that arginine would be an "appropriate substitution for lysine in the contemplated amino acid positions." Applicant further points out that paragraph [0120] of Schambye teaches the removal of wild type lysine residues in the β-subunit for the purposes of avoiding glycosylation of an internal lysine residue near the receptor binding site, citing paragraphs [0109], [0119] and [0120] of Schambye. Thus, Applicant concludes that by substituting the lysine for an arginine, one is effectively removing a glycosylation site. Therefore, one of ordinary skill in the art would have most certainly not substituted an arginine for the lysines at positions 2, 4, 64, 67 and 69 of Schambye since adding an arginine instead of a lysine at these positions would not allow for the intended glycosylation of the FSHβ-subunit.

These arguments have been fully considered, but are not found persuasive. First, paragraph [0120] Schambye teaches "a modified FSH-α and/or a modified FSH-β, which differs from the corresponding hFSH-α/β in at least one introduced and at least one removed lysine residue," wherein the removal of a lysine residue is selected from "the group consisting of K45(a), K63(a), K75(a), K91(a) K46(b), K54(b), K86(b), and

K110(b)," and further that "the removal preferably being achieved by substitution by any other amino acid residue, in particular by an arginine residue." As noted in the emphasis added above by the Examiner, Schambye explicitly teaches residue 63 of the β-subunit can be substituted with arginine, and residue 63 of the β-subunit is recited in instant claims 1, 84, 104 and 120 as a residue that can be substituted with arginine. Thus there is an explicit teaching in the prior art of Schambye that overlaps with the independent claims, namely substitution of arginine for lysine in residue 63.

Second, paragraph [0120] also teaches insertion of lysine residues and further that lysine and arginine represent preferred conservative amino acid substitutions (see paragraph [0044]). The person of ordinary skill in the art would be motivated to make the substitutions based upon the general teachings of Schambye. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art, namely, greater potency of the FSH analogs, cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In short, even though Schambye has a different motivation for adding and/or removing lysine residues, the structure of the modified FSH α- and β-subunits that one of ordinary skill in the art would arrive at, upon reading the combined teachings of Szkudlinski and Schambye, would be the same. Third, regarding the argument that the introduction of arginine would not lead to the introduction of glycosylation sites and therefore would not be expected to enhance stability, Applicant has offered only argument, but no evidence that this is so. Again, Nissen et al. (U.S. Patent No. 6,555,660, issued 29 April 2003) teaches at

column 5, that arginine is a possible amino acid for attachment of an oligosaccharide moiety.

Conclusion

Claims 1-6, 11, 12, 15, 26-28, 40, 43, 52, 58, 67, 84-93, 95, 97-99, 104-109, 111, 113-115, 120-123, 127-129 and 136-138 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BORGEEST whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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